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Triazole-Gold-Promoted, Effective Synthesis of Enones from Propargylic Esters and Alcohols: A Catalyst Offering Chemoselectivity, Acidity and Ligand Economy

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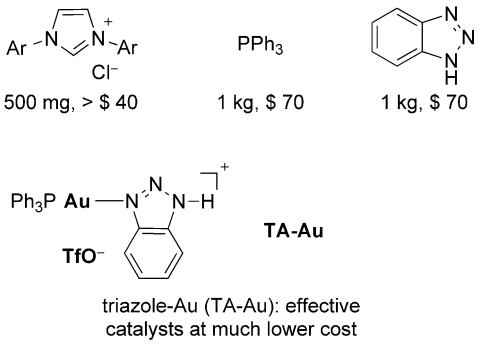
Abstract: The air, moisture and thermally stable 1,2,3-triazole coordinated gold(I) complexes (TA-Au) were revealed as the effective catalysts in promoting propargylic ester rearrangement and sequential allene hydration, giving the enones with excellent yields (up to 97% yields, 0.2% loading). The catalysts could also catalyze the more challenging Meyer–Schuster rearrangement (0.5% loading, up to 98% yields). The reported reaction confirmed TA-Au as a chemoselective catalyst in promoting alkyne activation with high efficiency and improved ligand economy.

Keywords: allenes; enones; Meyer–Schuster rearrangement; propargylic ester rearrangement; triazole gold complexes

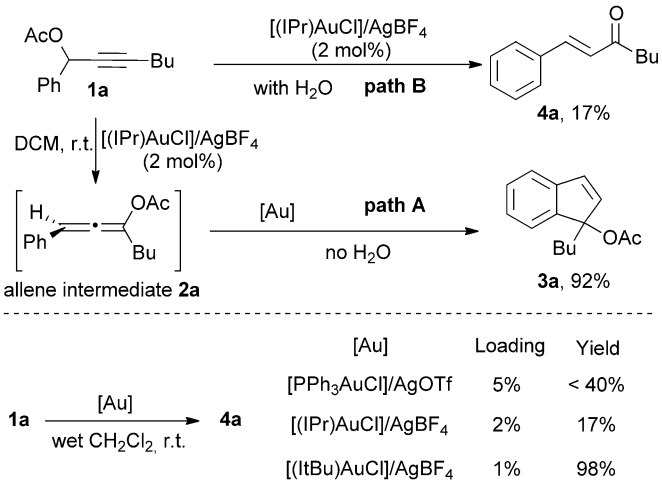
Homogenous gold catalysis has gained tremendous interests during the last decade due to its high efficiency in C/C multiple bond activation.[1] Similar to other transition metal complexes, ligands played a critical role in tuning the catalyst reactivity. One good example is the N-heterocyclic carbene (NHC) bound Au(I) complexes, which have gained great attention in this fast developing research field.[2] The different reactivity of the $[NHC\text{-}Au]^+$-based catalysts[3] relative to the simple $[PR_3\text{-}Au]^+$-based catalysts toward alkyne and alkene activation made them one of the most popular systems in homogenous gold catalysis. Recently, our group reported the synthesis and characterization of the 1,2,3-triazole-bound gold complexes (TA-Au) as effective catalysts toward the alkyne activation.[4] This new class of catalysts exhibited significantly improved thermal and substrate stability. These results opened up a new strategy in tuning gold reactivity through the counter ligand instead of the primary ligand. Herein, we report the application of the 1,2,3-triazole[5]-coordinated PPh_3-Au catalysts (TA-Au) in promoting the propargylic ester rearrangement and sequential hydration to form the enone with high efficiency (0.2% catalyst loading, up to 97% isolated yields), unique reactivity (combining the chemoselectivity and acidity) and improved ligand-economy (usea the much cheaper triazole and PPh_3 ligands as compared with NHC ligands). In addition, with the significantly improved thermal stability, TA-Au was further applied as the effective catalyst in promoting the the propargylic alcohol Meyer–Schuster rearrangement[6] to give the enones (0.5% catalyst loading, up to 98% yields), which highlighted the strength of this complex compared with other conventional $L\text{-}Au^+$ catalysts.

As indicated in Scheme 1, one advantage of the TA-Au catalyst is the significantly lower cost of the ligands. Compared with the NHC ligands, the combination of the PPh_3 primary ligand and triazole counter ligand can be >1000 times cheaper than the NHC primary ligand. Our original intention was to test whether TA-Au could promote transformations that previously required the expensive NHC primary ligands (to improve the ligand economy of the overall reaction). This initiated our investigation on the enone synthesis from the propargylic esters with our TA-Au catalyst.

The gold-catalyzed propargylic ester 3,3-rearrangement is a well-studied transformation.[7] One application of this process was the synthesis of enones from sequential hydration of the allene-acetate **2a** intermediates (Scheme 2, path B).[8] Although this direct

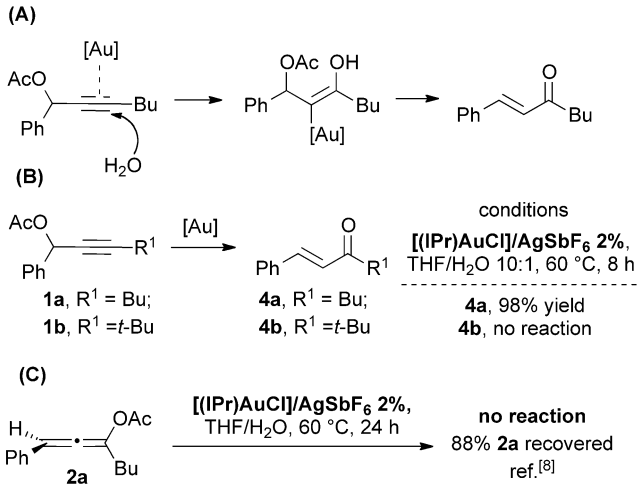


Scheme 1. NHC: good ligands in gold catalysis but at high cost.



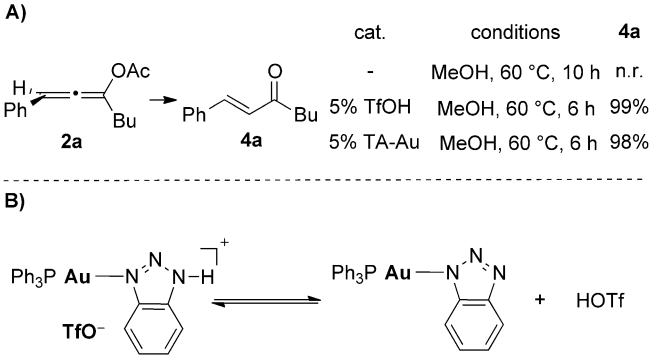
Scheme 2. L-Au$^+$: effective catalysts activating both alkyne and allene.

transformation provided one attractive strategy in preparing enones under mild conditions, it suffered from limited substrate scope due to the side reactions caused by the gold-promoted allene activation. One side reaction was the intramolecular Friedel–Crafts cyclization of **2a**, giving the indene **3a**.[9] As a result, a simple Au(I) catalyst, such as PPh_3Au^+, gave poor overall yields of the desired enones (5% Ph_3PAuCl/AgOTf, $<40\%$ yields, Scheme 2). To overcome this problem, Nolan and co-workers investigated different N-heterocyclic carbene ligands.[10] The more steric hindered [(ItBu)Au]$^+$ complex was revealed as the optimal catalyst for the formation of enones with high efficiency (1% loading, up to 98% yields). The authors have performed comprehensive mechanistic investigations.[8] Through both experimental and computational studies, the S_N2' water addition to the gold-activated alkyne was suggested as the mechanism by avoiding the formation of allene [Scheme 3(**A**)]. This mechanism was further supported by two other experimental observations: (i) no enone formation was observed with *t*-Bu-substituted alkyne **1b** [Scheme 3 (**B**)], and (ii) treating allene ester **2a** with the NHC-Au catalyst did not give enone **4a** [Scheme 3 (**C**)].



Scheme 3. Proposed S_N2' addition mechanism by Nolan.

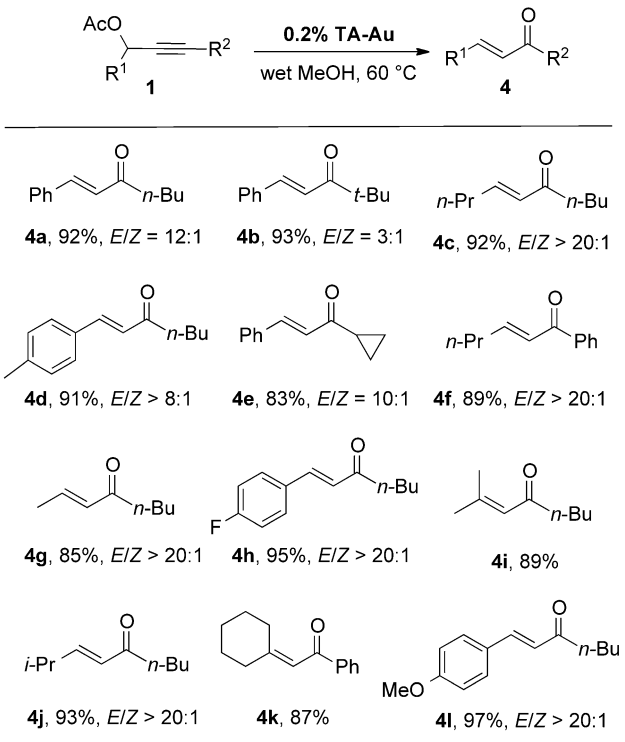
Recently, we reported the synthesis of *E*-α-iodoenone from a propargylic ester 3,3-rearrangement followed by the iodination of the allene ester. Interestingly, while all other [L-Au]$^+$ catalysts (such as [NHC-Au]$^+$ and [PPh_3-Au]$^+$) gave only the thermodynamically stable *Z*-isomers, the application of TA-Au led to the selective formation the kinetically favored *E*-isomers.[4c] These results suggested that TA-Au was a chemoselective catalyst, which could effectively promote alkyne activation without interrupting the inherent reactivity of the allene intermediates. Moreover, as shown in Scheme 4 (**A**), although the allene ester **2a** was rather stable even at elevated temperatures, treatment of this compound with a catalytic amount of acid could effectively convert the allene to the desired enones with excellent yields. Interestingly, unlike the previously reported NHC-Au complexes [Scheme 3 (**C**)], TA-Au could effectively catalyze the hydration of **2a** at either room temperature or elevated temperature, giving the desired enone in excellent yields. This was likely caused by the equilibrium



Scheme 4.

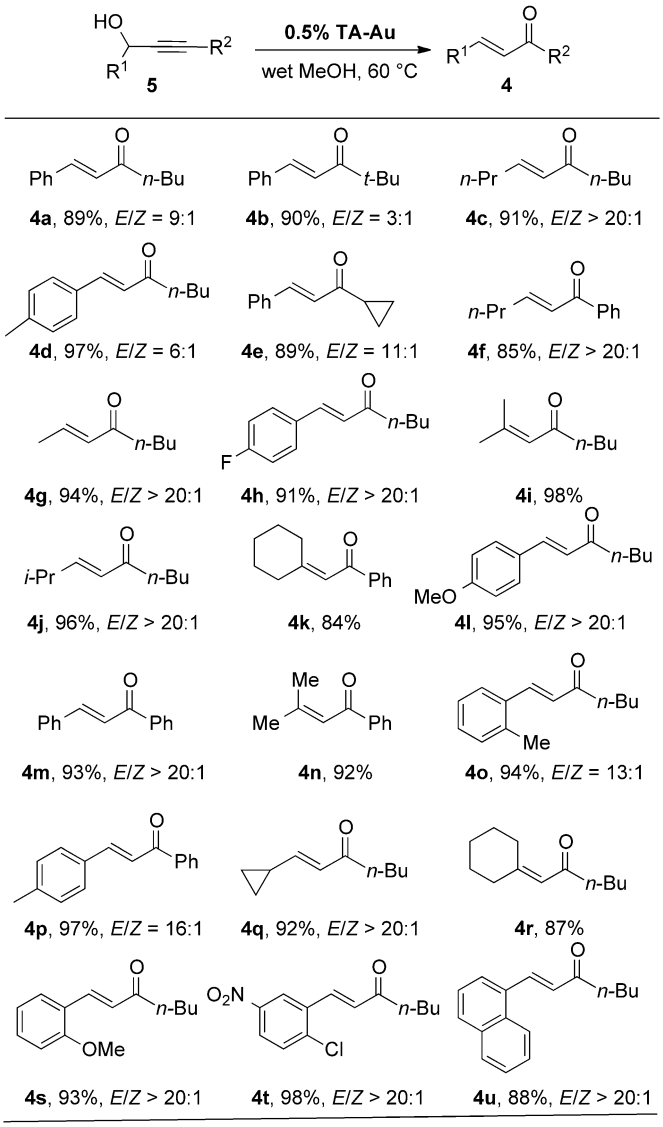
shown in Scheme 4 (**B**), where a catalytic amount of HOTf was released to serve as the Brønsted acid in promoting the hydration. We then postulated that TA-Au might be the effective catalyst in promoting the propargylic ester rearrangement and hydration to give enones. Unlike the previously reported $[(ItBu)Au]^+$ catalyst, TA-Au promoted this reaction through a chemoselective rearrangement followed by an effective hydration with the same pre-catalysts, which therefore provides an alternative to prepare enones compared with the S_N2' mechanism by the more expensive $[(ItBu)Au]^+$ catalysts

As expected, with the TA-Au catalyst, enone **4** was obtained in excellent yields. No indene by-products were observed, which highlighted the chemoselective nature of the TA-Au catalyst. TfOH was not a suitable catalyst for this reaction since the 3,3-rearrangement did not occur with only TfOH. Screening of solvents revealed MeOH as the optimal choice. The reaction worked smoothly at room temperature and gave the enone product in excellent yields over 24 h. Raising the temperature decreased the reaction time to 3–6 h (see detailed reaction condition screening in the supporting information). As a result, the enones **4** were obtained with near quantitive yields (>99% NMR yields) at very low catalyst loading (0.2%). As shown in Scheme 5, the reaction tolerated large group substrates, giving the desired enone in excellent yields and good double-bond selectivity (dominant *trans*-isomers). The *t*-Bu-substituted alkyne **2b**, which was not suitable with the NHC-Au catalyst due to the S_N2' mechanism, proceeded smoothly under these alternative conditions although with slightly decreased *Z/E* selectivity (**4b**). The high efficiency makes TA-Au a very attractive and practical catalyst for this transformation: at least 5 times lower catalyst loading than NHC-Au^+ with much less expensive ligands.



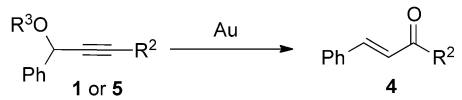
[a] *General reaction condition:* **1** (1.0 equiv.) and TA-Au (0.2 mol%) in wet MeOH (0.25 M), the reactions were monitored by TLC (3 - 6 h), 60 °C.
[b] Isolated yields; *E/Z* ratios were determined by ^{1}H NMR.

Scheme 5. TA-Au-catalyzed propargyl ester hydrolysis.[a,b]



[a] *General reaction conditions:* **5** (1.0 equiv.) and TA-Au (0.5 mol%) in wet MeOH (0.2 M), the reactions were monitored by TLC (4 – 12 h), 60 °C.
[b] Isolated yields; *E/Z* ratios were determined by ^{1}H NMR.

Scheme 6. TA-Au-catalyzed Meyer–Schuster arrangement.[a,b]



1 or **5** → **4**

1a:	[(IPr)AuCl]/$AgSbF_6$ (2.0%): 98% yield, Ref.[8]
R^3 = Ac, R^2 = *n*-Bu	(IPr)AuOH (2.0%): 91% yield, Ref. [6f]
	TA-Au (0.2%): 92% yield.
1b:	[(IPr)AuCl]/$AgSbF_6$ (2.0%): no reaction, Ref.[8]
R^3 = Ac, R^2 = *t*-Bu	**TA-Au (0.2%): 93% yield.**
5a:	(IPr)AuOH (2.0%): 97% yield, Ref.[10]
R^3 = H, R^2 = *n*-Bu	**TA-Au (0.5%): 89% yield.**
5b:	(IPr)AuOH (2.0%): 75% yield, Ref.[10]
R^3 = H, R^2 = *t*-Bu	**TA-Au (0.5%): 90% yield.**

Scheme 7. Comparison with the best results obtained in the literature.

Heating the [(IPr)AuCl]/$AgBF_4$ in wet MeOH at 60 °C produced a black solution/participate within 30 min, indicating the rapid decomposition of the catalyst. TA-Au, on the other hand, showed much improved stability, with no decomposition after more than 6 h under the same conditions. Considering the good thermal stability of TA-Au, we wondered whether this catalyst could also be used to promote the challenging Meyer–Schuster arrangement of propargylic alcohols **5** at higher temperature.[11] Impressively, the desired enone products were formed with excellent yields. The reaction tolerated a large group of substrates (Scheme 6). Surprisingly, the bulky *tert*-butyl-substituted alkyne **5b** was also suitable for this reaction, which suggested the effective water addition to the sterically hindered alkyne at higher temperature. The terminal alkyne[12] propargylic alcohol gave enals in modest yields,[13] which were likely caused by the longer reaction time required for the unfavored anti-Markovnikov addition. Continuous addition of catalysts could improve the overall yields. Nevertheless, the feasibility of this challenging substrate highlighted the strength of the TA-Au catalyst over the $[NHC\text{-}Au]^+$ catalysts (Scheme 7) by tolerating the much harsher conditions.[14]

In conclusion, we have reported herein the application of triazole-coordinated Au(I) complex (TA-Au) as effective catalyst in promoting propargylic ester rearrangement and hydration for the synthesis of substituted enones. The key for the success of the TA-Au catalyst was the combination of the unique chemoselectivity and acidity. Extension of this transformation to the Meyer–Schuster rearrangement by taking advantage of the thermal stability of the TA-Au further improved the atom economy. Compared with the more expensive NHC-Au catalysts, TA-Au promoted the reaction through a different mechanism and achieved better performance with lower overall costs.

Experimental Section

Typical Experimental Procedure

To a solution of **1a** (288 mg, 1.25 mmol) in wet MeOH (5 mL, 0.25 M, MeOH:H_2O = 100:1) was added Au(I) catalyst (1.8 mg, 0.0025 mol, 0.2 mol%). The reaction mixture was stirred at 60 °C. After the reaction was completed (4 h) according to TLC, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:20, v/v) to give **4a** as a colorless oil; yield: 92%.

Acknowledgements

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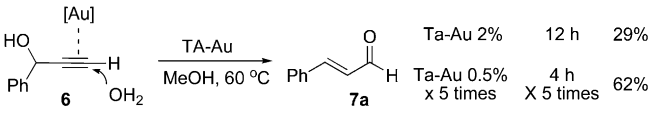
[11] Significant TA-Au catalyst decomposition was observed while treating with **4a** over time (after 30 h) even at room temperature.

[12] It is known that the gold cations decompose faster in the presence of terminal alkynes. The ^{31}P NMR investigation of gold(I) decomposition in terminal alkyne has been reported in ref.[4]

[13] Reaction of a terminal propargylic alcohol gave poor yields due to the undesired *anti*-Markovnikov addition.



[14] The allene ester from the TA-Au propargylic ester **1** catalyzed 3,3-rearrangment has been recently isolated, which confirmed the suggested rearrangement-hydration mechanism. See: D. Wang, L. N. S. Gautam, C. Bollinger, A. Harris, M. Li, X. Shi, X. *Org. Lett.* **2011**, *13*, 2618–2621.

